



Heart failure as a strong independent predictor of delirium after pacemaker operations☆



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ABSTRACT

Background: Postoperative delirium is a common and serious condition in the clinical setting that has been linked to increased mortality and worse outcomes. Some patients after pacemaker operations may suffer from delirium; however, this condition has not been clarified. The aim of this study was to investigate the prevalence and predictors of delirium after pacemaker operations such as initial permanent pacemaker implantation or pacemaker generator replacement.

Methods: We retrospectively evaluated 192 consecutive patients who underwent pacemaker operations. According to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria, patients were divided into two groups: patients with delirium and patients without delirium after pacemaker operation. The two groups were compared in terms of patient characteristics, clinical settings, and environmental factors.

Results: Forty patients (20.8%) suffered from delirium after pacemaker operations and were significantly older than patients without delirium (85.3 ± 6.4 years vs. 80.8 ± 8.4 years, $p = 0.0014$). Temporary pacing before permanent pacemaker implantation (30% vs. 11%, $p = 0.0019$) and intensive care unit admission (28% vs. 12%, $p = 0.014$) were more common in patients with delirium. Moreover, patients with delirium had more frequent heart failure than patients without delirium (78% vs. 41%, $p < 0.0001$). Multiple regression models showed heart failure as an independent predictor of delirium after pacemaker implantation.

Conclusions: Delirium after pacemaker operations was not uncommon and heart failure was a strong independent predictor of such a condition.

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1. Introduction

Delirium is the most common psychiatric disorder after cardiac-related operations, and the risk factors for its development are complex and multifactorial [1–7]. Clinical studies revealed that postoperative delirium is associated with prolonged and more costly hospital stay [8–10], impaired cognition [11–14], and worse clinical outcomes [14–16]. Therefore, prediction of postoperative delirium could be useful for clinical management. However, delirium after pacemaker operations has not been addressed. Therefore, the aim of the present study was to clarify the prevalence and contributing factors to the development of delirium after pacemaker operations.

2. Methods

2.1. Study population

This study was a retrospective evaluation of 192 consecutive patients who underwent pacemaker operations (109 permanent pacemaker implantations and 83 generator replacements) in Kitaishikai Hospital between July 2010 and September 2014. Our institution did not perform both the biventricular pacemaker implantation and implantable cardioverter-defibrillator (ICD). Therefore, there was no case undergoing biventricular pacing and/or ICD including generator replacement of these in the present study. All pacemakers in the present study were 2 single-chamber atrial pacemakers, 32 single-chamber ventricular pacemakers, and 158 dual-chamber pacemakers. 109 permanent pacemaker implantations were performed due to sinus node dysfunction ($n = 34$) or atrioventricular block ($n = 75$). Informed consent was obtained and the institutional review board of the hospital approved the retrospective use of the patients' data.

☆ The authors have no conflicts of interest to disclose.

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2.2. Pacemaker operations and delirium

Pacemaker operations were defined as initial permanent pacemaker implantation or pacemaker generator replacement. Delirium was defined as using an algorithm based on the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria [17]. In brief, postoperative delirium was diagnosed as disturbances of consciousness and acute change in cognition, or development of a perceptual disturbance after operation. According to the criteria, patients were divided into two groups: patients with delirium after operation (delirium group), and patients without delirium after operation (non-delirium group). The two groups were compared in terms of patient characteristics, clinical settings, and environmental factors.

2.3. Diagnosis of heart failure before pacemaker operations

Heart failure was defined as a combination of the presence of the typical signs or symptoms of heart failure, such as breathlessness at rest or during exertion, ankle edema and pulmonary crepitations, and confirmation by objective evidence of cardiac dysfunction (chest X-ray, echocardiography). This definition is according to the previously reported guideline [18]. Two experienced cardiologists, H.H. and S.L., who were blinded to the subjects' identity and clinical profile, evaluated the chest X-ray images. In addition, patients who had been under medical treatment for heart failure before admission were included. Before pacemaker operation, all patients were administered with 7.5 mg of pentazocine and 12.5 mg of hydroxyzine pamoate intramuscularly for sedation.

2.4. Statistical analysis

Data analysis was performed using StatView 5.0 (SAS institute, Cary, North Carolina) and SPSS version 20.0 (SPSS, Inc., Chicago, Illinois). Categorical variables are presented as number and percentage. Continuous variables are expressed as mean \pm standard deviation. The patient characteristics were compared using the Mann–Whitney test for continuous variables, and Chi-square test for categorical variables. Univariate regression analysis was performed to determine the contributing factors of delirium after pacemaker operations using simple logistic regression with the odds ratio and 95% confidence interval. Multiple regression analysis was performed to evaluate the independence and robustness of heart failure using different models: utility (age, intensive care unit admission, temporary pacing, heart failure), laboratory (age, albumin, HDL-C, heart failure), comorbidity (age, previous PCI, dementia, heart failure), and cardiac function (age, LVEF, heart failure). Covariates were entered into each model on the basis of associations in the univariate analysis with p values < 0.05 . Harrell's C statistic and Model Chi-square were used to evaluate the model [19]. Values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Clinical characteristics and history

The patients' clinical characteristics and history are shown in Table 1. The study population comprised 192 patients: 109 of them received initial permanent pacemaker implantation and 83 of them received generator replacement operation. There were 40/192 (20.8%) patients who suffered from postoperative delirium. The delirium group was significantly older than the non-delirium group (85.3 ± 6.4 years vs. 80.8 ± 8.4 years; $p = 0.0014$). Gender, body mass index, and coronary risk factors (i.e., hypertension, dyslipidemia, diabetes, and smoking history) did not differ between the two groups. The frequency of developing delirium was markedly higher in patients with heart failure than those without heart failure (78% vs. 41%, $p < 0.0001$).

Table 1

Clinical characteristics of patients who underwent pacemaker operation ($n = 192$).

Variable	Delirium (+) ($n = 40$)	Delirium (–) ($n = 152$)	p value
Initial pacemaker implantation	23 (58)	86 (57)	0.92
Age (years)	85.3 ± 6.4	80.8 ± 8.4	0.0014
Male sex	19 (48)	64 (42)	0.54
Body mass index (kg/m^2)	23.2 ± 2.9	23.1 ± 3.5	0.89
Hypertension	32 (80)	120 (79)	0.88
Hyperlipidemia	24 (60)	72 (47)	0.16
Smoking history (current or former)	12 (30)	45 (30)	0.96
Current cigarette use	1 (3)	7 (5)	0.55
Diabetes	18 (45)	51 (34)	0.18
Chronic kidney disease	25 (63)	95 (63)	–
Patient history			
Previous coronary artery bypass graft surgery	1 (3)	4 (3)	0.96
Previous percutaneous coronary intervention	7 (18)	7 (5)	0.0053
Previous stroke	7 (18)	25 (16)	0.87
Dementia	12 (30)	21 (14)	0.016
Any arterial fibrillation or flutter ^a	13 (33)	37 (24)	0.30
Heart failure	31 (78)	63 (41)	< 0.0001
Left ventricular ejection fraction (%)	57.6 ± 13.1	62.6 ± 10.7	0.025

Values are expressed as mean \pm SD or n (%).

^a Includes paroxysmal arterial fibrillation or flutter.

3.2. Baseline characteristics and operation-related data

The baseline characteristics of patients on admission are shown in Table 2. Postoperative delirium was more frequent in patients admitted to the intensive care unit compared with the patients who were not admitted to the intensive care unit (28% vs. 12%, $p = 0.014$). The number of days from admission to operation and operation time were not different between the two groups. The time of operation was significantly longer in the patients with permanent pacemaker implantation compared with generator replacement (99.5 ± 30.3 min vs. 53.0 ± 27.4 min; $p < 0.0001$). However, the operation time in the delirium group was almost similar to that in the non-delirium group ($79.2 \pm$

Table 2

Baseline characteristics and operation-related data ($n = 192$).

Variable	Delirium (+) ($n = 40$)	Delirium (–) ($n = 152$)	p value
Intensive care unit admission	11 (28)	18 (12)	0.014
Temporary pacing before operation	12 (30)	16 (11)	0.0019
Heart rate (number/min)	59.9 ± 21.7	56.5 ± 17.0	0.43
Systolic blood pressure (mmHg)	140.7 ± 26.3	139.9 ± 26.4	0.84
Diastolic blood pressure (mmHg)	67.0 ± 14.8	65.2 ± 14.9	0.85
Laboratory data			
Albumin (g/dL)	3.7 ± 0.5	3.8 ± 0.4	0.050
Hemoglobin (g/dL)	11.8 ± 1.4	12.7 ± 7.7	0.20
Total bilirubin (mg/dL)	0.6 ± 0.3	0.6 ± 0.2	0.69
Fasting glucose (mg/dL)	110.1 ± 36.8	99.6 ± 31.0	0.027
Hemoglobin A1c (%)	5.9 ± 0.8	5.8 ± 0.7	0.22
Total cholesterol (mg/dL)	161.1 ± 34.0	167.9 ± 33.0	0.25
High density lipoprotein cholesterol (mg/dL)	47.9 ± 13.1	52.9 ± 12.7	0.037
Triglyceride (mg/dL)	97.4 ± 44.2	94.8 ± 43.5	0.61
Low density lipoprotein cholesterol (mg/dL)	93.7 ± 27.7	96.3 ± 27.9	0.45
Brain natriuretic peptide (pg/mL)	367.3 ± 420.8	309.2 ± 501.2	0.050
Days from admission to operation (days)	3.4 ± 4.5	3.2 ± 4.9	0.60
Operation time (min)	79.2 ± 42.9	79.4 ± 35.5	0.72
Use of sleeping drug the day before operation	17 (43)	64 (42)	0.96
Use of sedation just before operation	40 (100)	152 (100)	–

Values are expressed as mean \pm SD or n (%).

42.9 min vs. 79.4 ± 35.5 min; $p = 0.72$). In addition, delirium after pacemaker operations occurred equally in permanent pacemaker implantation and generator replacement (58% vs. 57%; $p = 0.92$). There were 28/192 (15%) patients who underwent temporary pacemaker placement before permanent pacemaker implantation because of bradycardia; these patients developed the delirium more frequently compared with patients without temporary pacing (30% vs. 11%, $p = 0.0019$).

3.3. Independent predictors for postoperative delirium

Univariate regression analysis for postoperative delirium was given in Table 3. Multiple regression models showed that heart failure was consistently significant in every model, and odds ratios were similar (3.39–3.97), indicating an independent factor of postoperative delirium (Table 4).

4. Discussion

The main findings in the present study were as follows: (1) The prevalence of delirium after pacemaker operations was 20.8%. (2) In addition to age, which is generally recognized as a predictor of delirium, heart failure was a strong independent predictor of subsequent delirium after pacemaker operations.

Table 3
Univariate regression analysis for prediction of delirium after pacemaker operations.

Variable	Odds ratio	95% confidence interval	p value
Initial pacemaker implantation	1.04	0.51–2.10	0.92
Age (years)	1.08	1.03–1.14	0.0026
Male sex	1.24	0.62–2.50	0.54
Body mass index (kg/m^2)	1.01	0.91–1.12	0.89
Hypertension	1.07	0.45–2.54	0.88
Hyperlipidemia	1.67	0.82–3.38	0.16
Smoking history (Current or Former)	1.02	0.48–2.18	0.96
Current cigarette use	0.53	0.06–4.45	0.56
Diabetes	1.62	0.80–3.29	0.18
Chronic kidney disease	1.00	0.49–2.05	–
<i>Patient history</i>			
Previous coronary artery bypass graft surgery	0.95	0.10–8.73	0.96
Previous percutaneous coronary intervention	4.39	1.44–13.38	0.0092
Previous stroke	1.08	0.43–2.71	0.87
Dementia	2.67	1.18–6.06	0.019
Any arterial fibrillation or flutter ^a	1.50	0.70–3.20	0.30
Heart failure	4.87	2.17–10.93	0.0001
Left ventricular ejection fraction (%)	0.97	0.94–0.99	0.017
Intensive care unit admission	2.82	1.21–6.61	0.017
Temporary pacing before operation	3.64	1.55–8.54	0.0029
Heart rate (number/min)	1.01	0.99–1.03	0.29
Systolic blood pressure (mmHg)	1.00	0.99–1.01	0.87
Diastolic blood pressure (mmHg)	1.01	0.99–1.03	0.49
<i>Laboratory data</i>			
Albumin (g/dL)	0.36	0.15–0.85	0.019
Hemoglobin (g/dL)	0.88	0.69–1.11	0.28
Total bilirubin (mg/dL)	1.63	0.45–5.92	0.46
Fasting glucose (mg/dL)	1.01	1.00–1.02	0.078
Hemoglobin A1c (%)	1.28	0.81–2.00	0.29
Total cholesterol (mg/dL)	0.99	0.98–1.01	0.25
High density lipoprotein cholesterol (mg/dL)	0.97	0.94–1.00	0.031
Triglyceride (mg/dL)	1.00	0.99–1.01	0.74
Low density lipoprotein cholesterol (mg/dL)	1.00	0.98–1.01	0.60
Brain natriuretic peptide (pg/mL)	1.00	1.00–1.00	0.51
Days from admission to operation (days)	1.01	0.94–1.08	0.77
Operation time (min)	1.00	0.99–1.01	0.97
Use of sleeping drug the day before operation	1.02	0.50–2.06	0.96

^a Includes paroxysmal arterial fibrillation or flutter.

4.1. The prevalence of delirium after pacemaker operations

Delirium is a common complication that occurs after cardiac-related operations. In this study, post-pacemaker operation delirium incidence was 20.8%, whereas the frequency of delirium after open heart surgery ranged from 3% to 73% [2,20,21]. Although pacemaker operation is a less invasive procedure than open heart surgery, the occurrence of postoperative delirium is still common. Previous studies suggested age, atrial fibrillation [20,22,23], history of stroke [1,21,23], urgent operation [23], and abnormal albumin level [7], as possible contributing factors to delirium after cardiac surgery. Most studies demonstrated that age is a pivotal contributor to the occurrence of delirium not only after open heart surgery, but also after other operations [20,22,24,25]. Moreover, previous studies demonstrated that pacemaker implantation could be associated with the development of postoperative delirium, especially in elderly patients. Our present data consisted of these reports [26,27]. In one of these reports, frequency of delirium after pacemaker implantation was 8.3% [27], while it was much higher, up to 20.8%, in the current study. The relatively high median age of 83 years may have influenced the high prevalence of delirium after pacemaker operations in the present study.

4.2. The association between heart failure and postoperative delirium

Previous studies suggest the possible association between heart failure and postoperative delirium in patients undergoing (1) major elective non-cardiac and non-neurological surgery [28]; (2) coronary artery bypass grafting (CABG), valve replacement and/or valve repair, and CABG plus valve replacement and/or valve repair [29]; and (3) transcatheter aortic valve implantation [30]. The present study firstly demonstrated that heart failure is an independent predictor of delirium after pacemaker operations, with high odds ratios. Although the direct link between heart failure and postoperative delirium remains unclear, recent studies indicate cognitive impairment as a possible explanation [31]. Preoperative cognitive impairment is generally considered as a contributing factor for postoperative delirium among older patients [32–34]. In a cohort study on cardiac surgery, Kazmierski et al. revealed that preoperative cognitive impairment, assessed by a mini-mental state examination (MMSE), was the strongest independent risk factor for postoperative delirium [22]. In addition, some studies demonstrated that cognitive impairment was commonly observed, and was associated with the severity of heart failure [35–38]. Studies focused on the relationship between cerebral hypoperfusion and cognitive impairment in patients with heart failure [39,40], but the mechanism is not totally understood. In heart failure, low cardiac output, low systolic blood pressure, and impaired cerebral neurohormonal auto-regulatory mechanisms may induce the reduction of cerebral blood flow [41]. Gruhn et al. observed, by single-photon emission computed tomography (SPECT), a marked reduction of cerebral blood flow in patients with severe heart failure [40]. These studies support our new insight, but further investigations are needed to clarify the underlying mechanism of postoperative delirium in patients with heart failure.

4.3. Study limitations

This study has several limitations. A major limitation is the single-center, retrospective design. The study population was relatively small in number, but it was sufficient to determine the independent predictor of delirium, which was the primary aim of the study. In addition, baseline cognitive function, which is considered a risk factor for postoperative delirium, was not objectively evaluated.

5. Conclusion

The prevalence of delirium after pacemaker operations was not uncommon and heart failure was a strong independent predictor of such a condition. To clarify whether some interventions can prevent the

Table 4

Multiple regression models for prediction of delirium after pacemaker operations.

Variables	Utility model (Model Chi-square = 29.1, c-statistics = 0.77) OR (95% CI), p value	Laboratory model (Model Chi-square = 24.7, c-statistics = 0.75) OR (95% CI), p value	Comorbidity model (Model Chi-square = 29.6, c-statistics = 0.76) OR (95% CI), p value	Cardiac function model (Model Chi-square = 25.5, c-statistics = 0.76) OR (95% CI), p value
Age (per 1 year increase)	1.06 (1.01–1.12) p = 0.03	1.05 (0.99–1.11) p = 0.08	1.06 (1.00–1.12) p = 0.0549	1.07 (1.02–1.13) p = 0.01
Intensive care unit admission	1.12 (0.35–3.62) p = 0.85			
Temporary pacing	2.95 (0.93–9.32) p = 0.07			
Albumin (per 1 g/dL increase)		0.77 (0.30–1.97) p = 0.58		
HDL-C (per 1 mg/dL increase)		0.98 (0.95–1.01) p = 0.28		
Previous PCI			3.92 (1.17–13.1) p = 0.03	
Dementia			2.08 (0.83–5.22) p = 0.12	
LVEF (per 1% increase)				0.97 (0.94–1.01) p = 0.12
Heart failure	3.97 (1.70–9.31) p < 0.01	3.79 (1.63–8.81) p < 0.01	3.62 (1.56–8.42) p < 0.01	3.39 (1.43–8.05) p < 0.01

OR = odds ratio, CI = confidence interval, HDL-C = high density lipoprotein cholesterol, PCI = percutaneous coronary intervention and LVEF = left ventricular ejection fraction.

Bold values indicate significance at $p < 0.05$.

development of delirium after pacemaker operations especially in patients with heart failure, further prospective studies are needed.

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